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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,552	GALLO ET AL.	
	Examiner	Art Unit	
	ANISH GUPTA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-2-06, 8-27-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-13, drawn to method of inhibiting the spread and/or reducing the risk of infection of a virus, classified in class 514, subclass 2.

II. Claims 14-25, drawn to method of treating atopic dermatitis, classified in class 514, subclass 2.

The inventions are distinct, each from the other because of the following reasons:

The products of Group I and Group II are independent and distinct because each method has a differing end points. A method of inhibiting the spread and/or reducing the risk if infection of a virus involves different patient populations and different end points form treating atopic dermatitius. Atopic dermatitus is an inflammatory disease that can be a result of many environmental agents such as allergens and bacteria. Method of treating the symptoms of this disease does not involve inhibiting infections of a virus. Thus the methods are independent and distinct. Furthermore, each would require and independent search. A search for treating atopic dermatitus would not lead to methods involving inhibiting the spread and/or reducing the risk of infection of a virus as a result of herpes virus or papilloma virus.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the

examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

This application contains claims directed to the following patentably distinct species

SEQ ID NO 13-28 in Groups I and III. And a polynucleotide that encodes SEQ ID NO 13-28 for Group II.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, 1-20 are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

During a telephone conversation with Joseph Baker on March 11, 2009 a provisional election was made without traverse to prosecute the invention of Group I, claim1-13. Affirmation of this election must be made by applicant in replying to this Office action. Claims 14-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any

amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicants also elected species of SEQ ID NO: 13. A search was conducted for the elected species and prior art was not found. In accordance with Markush practice the search was extended and no prior art was found. As a result, the election of species has been withdrawn. However the claims are rejected under 112 First Paragraph.

Claim Objections

2. Claim12 is objected to because of the following informalities: papilloma is misspelled in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or

absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) the nature of the invention

The invention relates to cathelicidin functional fragments and their use as antiviral agents.

(2) the state of the prior art

For viral vaccinations, it is well known in the art that there are significant obstacles in achieving the vaccination. For example, it is well known in there exist numerous obstacles to therapy of HIV infections. These include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus (see Siliciano et al); 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation.

Braun et al. teach HIV treatment remains a tremendous challenge. "Despite the availability of a diverse range of molecule strategies that are able to provide potent inhibition of HIV replication in the laboratory, translation of these *in-vitro* success to *in-vivo* therapies have been difficult." (see page 838 of Braun et al.). For HIV gene therapy, the reference states that "translation of these

effective *in-vitro* strategies to clinically efficacious treatments has remained problematic, in large part due to the inefficient techniques available to stably introduce these genes into the desired target cell population *in vivo*." The reference states that in-vitro studies, in HIV therapy, are conducted under highly idealized conditions that use population so cells that are >90% generically modified. These conditions are of "uncertain relevance for in-vivo replication." (see Braun page 844). Further, in-vitro experiments cannot adequately address issues such as immungenicity (see Braun page 845). Further, it is known that HIV will mutate and escape pharmacological therapy. "Inhibitors that have relatively short points of contact such as ribozymes and RNAi are more likely to be affected by sinble base mutation. Because of inherent limitations in the number of replication cycles and the size of the virus population studied, which differ on several orders of magnitude from those observed *in-vivo* settings, *in vitro* studies are likely to be a relatively insensitive means to rigorously asses the potential development of resistance" (Braun page 846). Gait et al. teach that that for RT and protease HIV therapy, many of the resistance mutants are found at sites that are far removed from the drug-binding sites, and operate by subtly changing the protein structure or reduce drug sensitivity with out conferring an absolute resistance (see page 437). "It will be important to determine whether the HIV-1 virus is equally adept at evading drugs that are adept at evading drugs that are directed against essential RNA targets, such as TAR and the RRE." (Gait page 437).

Gill et al. teaches that that the Herpes simplex virus establishes itself as a latent infection within the sensory ganglia and it is insured that the host will have a lifelong infection by allowing periodic reactivation, resulting the production of new virions (se page 36). The reference further states that there is a difficulty in developing a vaccine for the HSV-2 virus because HSV-2 infects a mucosal site. Most vaccines do not provide effective mucosal response. Kleymann states that the protection of skin and mucous membranes from viral infection is nearly impossible with respect to

HSV-1, but may be possible to some extent with use of condoms in the case of HSV-2 (see page 136). Vaccination against HSV has been evaluated since 1920s but a vaccing is not yet available for HSV infections (see page 139).

With respect to antiviral therapy, the art recognizes that antiviral therapy has been successful with HSV-1, HSV-2, VZV and CMV. However, human herpesvirus 6-9 and Epstein Barr virus, has achieve limited success (see page 128 of Field).

CDC fact sheet states that for genital human papillomavirus (HPV), there is no treatment for the virus itself. The vaccine available protects female form four types of HPV, however there is no vaccine for other types of the papillomavirus.

Finally, the specification acknowledged that the effect of cathelicidin functional fragments on vaccinia virus have not been reported (see page 34 of the specification).

(3) the relative skill of those in the art

The relative skill of those in the art is high.

(4) the predictability or unpredictability of the art

Given the state of the art of HIV therapy, the unpredictability of treating HIV infections is highly unpredictable. Similarly, obtaining a vaccine for HIV, herpes and papilloma and the like also is highly unpredictable.

(5) the breadth of the claims

The claims are drawn to a method of "inhibiting the spread and/or reducing the risk of infection of a virus comprising contacting a virus with an inhibiting effective amount of a cathelicidin functional fragment." Taken in its broadest reasonable interpretation, the claims as

written read on vaccines since the claims state "inhibiting the spread" and "reducing the risk" of the viral infection.

(6) the amount of direction or guidance presented; and (7) the presence or absence of working examples

The specification provides guidance on sixteen different fragments obtained from cathelicidin. These fragments share a significant homology and have the core sequence KRIVQRIKDFLRNLVP. The specification demonstrates the effectiveness of these fragments against different bacterial strains and fungal strains, specifically S. aureus, E.Coli, C. albicans (see page 46). The specification acknowledges that the effect of cathelicidin functional fragments on vaccinia virus have not been reported in the art.

While the specification discloses the use of the specific peptides (obtained from LL-37) for use against bacterial and fungus, the specification does not provide a single example or test result in of its effectiveness against any single virus. The specification hypothesizes the mechanism of action for these peptides to involve disruption of the microbial membrane and/or the penetration of the microbial membranes to interfere with intracellular functions. However, the specification does not demonstrate this hypothesis. The specification does not provide any evidence that the specific fragments disclose have the ability in "inhibiting the spread and/or reducing the risk of infection of a virus." It must not be forgotten that Applicants own specification states cathelicidin functional fragments on vaccinia virus have not been reported. Furthermore, the specification does not provide for a varity of fragments obtained form cathelicidin.

Treating viral infections is known to be difficult. For the treatment of HIV infections, for example, guidance is necessary since it is such a difficult disease to treat. Braun et al. illustrates that even where in-vitro data is present, such data is not sufficient to conclude the effectiveness of in

HIV treatment since *in-vitro* strategies do not give insight to techniques available to stably introduce these genes into the desired target cell population *in vivo*. Furthermore, the inherent limitations in the number of replication cycles and the size of the virus population studied, which differ on several orders of magnitude from those observed *in-vivo* settings, *in vitro* studies are likely to be a relatively insensitive means to rigorously asses the potential development of resistance. The disclosure fail to address concerns such as the inability to get high-level expression of the therapeutic of interest to inhibit HIV-1 infection, the therapeutic does interfere with normal cellular processes, the therapeutic is not immunogenic or eliminates of the target cell population, and if the therapeutic reaches those HIV-1 that resides in many reservoirs and are often refractory to standard therapeutics.

Similarly, the art recognizes a difficulty in developing a vaccine for the HSV-2 virus because HSV-2 infects a mucosal site. Most vaccines do not provide effective mucosal response. Kleymann states that the protection of skin and mucous membranes from viral infection is nearly impossible with respect to HSV-1, but may be possible to some extent with use of condoms in the case of HSV-2 (see page 136). Vaccination against HSV has been evaluated since 1920s but a vaccing is not yet available for HSV infections (see page 139).

Given the breath of the claims more guidance is required to practice the claimed invention. It is noted that the art has recognize the key target for all the successfil compound that are active against alphaherpesvirus, to date, is the virus encoded DNA-polymerase (see page 129 of Fields et al). and not the "microbial membrane." The specification does not provide any guidance, especially for the use against herpes virus, that the peptides target DNA-polymerase. Furthermore, guidance is necessary since the CDC state that there is no treatment for the virus itself. Without such guidance one would be burden with undue experimentation.

(8) the quantity of experimentation necessary

Given all of the factors, especially the state of the art coupled with the lack of guidance one would be burdened with undue experimentation to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

/Anish Gupta/
Primary Examiner, Art Unit 1654